In re Application of: Gila MAOR
Serial No.: 10/627,739
Filed: July 28, 2003
Office Action Mailing Date: August 13, 2008

Examiner: Barnhart, Lora Elizabeth
Group Art Unit: 1651
Attorney Docket: 26243

REMARKS

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 1-9 and 11-106 and 108 are in this Application. Claims 12, 13, 15, 16 and 24-103 were withdrawn from consideration. Claims 1-9, 11, 14, 17-23 and 108 have been rejected under 35 U.S.C. § 112 first paragraph. Claims 104-106 have been rejected under 35 U.S.C. § 102(b). Claims 1-5, 11, 14, 17-23 and 108 have been rejected under 35 U.S.C. § 103(a). Claim 6, 8 and 104-106 have now been canceled. Claims 1 and 9 have been amended herewith.

35 U.S.C. § 112, First Paragraph, Rejections

The Examiner has rejected claims 1-9, 11, 14, 17-23 and 108 under 35 U.S.C. 112, first paragraph, because while the specification, while being enabling for a method of generating cultured chondrocytes that express type II collagen but not type I collagen by using one specific set of culture conditions, does not reasonably provide enablement for doing so using any given and culture conditions.

Specifically, the Examiner states that the as-filed specification includes working examples in which mandibular condyles from neonatal tissue are harvested and the resulting cells are cultured in a culture medium (DMEM) supplemented with serum and ascorbic acid, β-glycerophosphate, calcium chloride and pyruvate and that culturing should be effected for at least 7 days.

Examiner's rejections are respectfully traversed. Claim 1 has now been amended. Claim 6 has been cancelled herewith.

Applicants point out that culturing media for chondrocytes are well known in the art and are routinely practiced and indeed are not part of the novelty of the claimed invention, which rather lies in the cell source (mandibular condyle). Similar chondrocyte culturing media are taught in the art. For example, Cheung in U.S. Pat.

4,757,017 teaches culturing in DMEM and serum (column 6 last paragraph); Schnabel (2002, cited by the Examiner) teach serum supplemented DMEM and ascorbic acid (page 63 left column, first paragraph, last 2 lines); Tubo in U.S. Pat. 5,723,331 teach serum supplemented DMEM (column 18 paragraph 3) and ascorbic acid (column 16 paragraph 4). In addition 5,723,331 which was published in 1998 (5 years prior to the present filing) specifically mentions that ascorbic acid enhances the production of cartilage specific proteoglycans and collagen. $CaCl_2$, β-glycerolphosphate and pyruvate are also routinely used in the art of cell-culturing. Pyruvate is routinely added as a source of energy (see Wikipedia http://en.wikipedia.org/wiki/Sodium_pyruvate, attached herewith), Calcium chloride is routinely used in cell culturing and may be added separately (as in this case) or provided with the commercially produced medium (e.g., DMEM). The cited art all included $CaCl_2$ in the culture medoium (see e.g., 5,723,331 indicates DMEM and not Ca-free DMEM, column 18 line 19; Landesberg et al. Calcif. Tissue Int (1995) 56:71-77 page 72 left column, second paragraph). β-glycerolphosphate is commonly used in chondrocytes cultures following endochondral ossification cascade (see Descalzi Cancedda F. et al. Hypertrophic chondrocytes undergo further differentiation in culture. Journal of Cell Biology. 117(2):427-35, 1992 Apr.; and Brown RA. et al Collagenase and gelatinase production by calcifying growth plate chondrocytes. Experimental Cell Research. 208(1):1-9, 1993 Sep, attached)

In view of the above, Applicants submit herewith that chondrocyte culturing media are known in the art and can be readily applied to the claimed teachings without undue experimentation.

With respect to the culturing period, Applicant wishes to point out that Schnabel (2002) presents typical cascade of events typical to development of chondrocytes derived from mature cartilage-five patients of average age of 84. Numerous publications show that cells separated from mature cartilage undergo irreversible dedifferentiation resulting in type I producing cells.

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In contrast developmental cascade of our model, proceed the other way round. Following a brief phase of intensively proliferation (positive PCNA) of chondrocytes precursor cells producing type I collagen – typical to normal chondroprogenitor cells, cells, being originated from growth center, differentiate spontaneously into type II collagen producing cells.

Notwithstanding the above, in results obtained following filing of the instant application but based on the present teachings, the present inventor was able to show re-differentiation following 3 days in culture (the results are supported by a declaration under 1.132 by inventor Gila Maor), clearly indicating that the cells were redifferentiated already after 3 days in culture albeit to a lesser extend.

In view of the above arguments and declaration, it is clear that the claimed invention is enabled.

However notwithstanding the above, in order to expedite prosecution of this case, Applicant has elected to add a limitation to claim 1, pertaining to plating the cells as a monolayer. Support for the added limitation can be found in page 51 line 20 ("*Cells, plated as a monolayer, were attached to the plate and started to proliferate.*").

In addition, culturing is effected for at least 7 days to allow re-differentiation of the cells to type II collagen expressing cells (this limitation as well supported in page 31 lines 1-2, and page 18 lines 11-12).

Applicant requests herewith withdrawal of the rejection in view of the above arguments, amendments and declaration.

The Examiner has rejected claims 6-9 under 35 U.S.C. 112, first paragraph. The Examiner states that there is no support for claim 6 and claims 7-9 depend therefrom. Examiner's rejection is respectfully traversed. Claims 6 and 8 have been cancelled herewith. Claim 1 has been amended such that "culturing comprises plating the cells as a monolayer", which is clearly supported (*supra*), as indicated by the Examiner. Applicant points out that claim 7 depends from claim 1 and claim 9 depends from claim 7 and not from rejected claim 6 as asserted by the Examiner.

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35 U.S.C. § 102

The Examiner rejected claims 104-106 under 35 U.S.C. 102(b) as being anticipated by Bhalerao et al (1995 Tissue and Cell 27:369-382).

Examiner's rejection is respectfully traversed. Claims 104-106 have been cancelled, without prejudice, thereby rendering moot Examiner's rejection in this case.

35 U.S.C. § 103

The Examiner rejected claims 1-5, 11, 14, 17-21, 23 and 108 under 35 U.S.C. 103(a) as being unpatentable over Cheung (4,757,017) in view of Bhalerao (1995 Tissue and Cell 27:369-382).

The Examiner states that a person of skills in the art would have had a reasonable expectation of success in substituting the mandibular condyles of Bhalerao et al. for the femoral condyles of Cheung and culturing said cells according to the art of Cheung.

Examiner's rejection is respectfully traversed. Claim 1 has been amended. Claim 6 has been cancelled herewith.

Currently amended claim 1 recites plating the cells as a monolayer (support for the added limitation is provided hereinabove). Such a plating procedure is not taught by the art of Cheung who clearly teaches using a 3 dimensional support (porous HA ceramic granules, see column 6 lines 29-30), which results in plating the cells attached to the scaffold as a multilayer and not attached to the plate substratum., namely not as a monolayer, as claimed.

In fact, Cheung clearly teaches away from plating the cells as a monolayer (see column 6 lines 10 to 17):

> *"However, when chondrocytes from avian and mammalian species are released from the cartilage matrix and grown in monolayer cell culture systems, they stop*

> *producing these characteristic molecules in a variety of situations (13-19). The collagen phenotype of the progeny of a cloned chondrocyte has been shown to change from type II to type I and type I trimer collagen during growth to senescence (20)."* (Emphasis Added)

Not withstanding the above, Applicants point out that the skilled artisan would not have been motivated to replace Cheung's cells with those of Bhalerao et al., since Bhalerao et al. clearly teach away from using mandibular condyle for culturing the claimed chondrocytes.

In fact Bhalerao et al. say that cells of a neonatal mandibular condyle differentiate in vitro to pro-osteoblasts (giving rise to bone-forming cells) and not chondrocytes.

See page 370, left column, 2nd paragraph:

> *"In vitro, however, the same system behaves quite differently. The progenitor zone, which in vivo produces chondroblasts, changes its mode of expression and gives rise to preosteoblasts which differentiate into osteoblasts and eventually form bone (Silbermann et al., 1983). "*

In view of the above claim amendments and arguments, it is Applicants position that the claimed invention is novel and non obvious over Cheung (4,757,017) in view of Bhalerao (1995 Tissue and Cell 27:369-382). Withdrawal of the rejection is respectfully requested.

The Examiner rejected claims 1-5, 11, 14, 17-23 and 108 under 35 U.S.C. 103(a) as being unpatentable over Tubo et al. (5,723,331) in view of Bhalerao (1995 Tissue and Cell 27:369-382).

The Examiner states that a person of skills in the art would have had a reasonable expectation of success in substituting the mandibular condyles of Bhalerao et al. for the articular cartilage of Tubo and culturing said cells according to the art of Tubo.

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The Examiner's rejection is respectfully traversed.

Applicant maintains that the Examiner has failed to establish a *prima facie* case of obviousness since the cultured chondrocytes taught by Tubo et al. do not follow the claimed recitation i.e., express Type 2 collagen but not Type I collagen. In fact according to Tubo, none of the cells obtained have the aforementioned signature. See Tables I and II: either the cells express Type 2 and Type I collagens, or Type I only but none express Type 2 collagen but not Type I collagen which is associated with true Hyaline cartilage.

Hence by failing to teach all the claimed elements, Applicant contends that a proper case of *prima facie* obviousness has not been made. Withdrawal of the rejection is respectfully requested.

In view of the above amendments and remarks it is respectfully submitted that claims 1-5, 7, 9, 11, 14, 17-23 and 108 are now in condition for allowance. A prompt notice of allowance is respectfully and earnestly solicited.

Respectfully submitted,

Martin D. Moynihan
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Date: December 15, 2008

Enclosures:

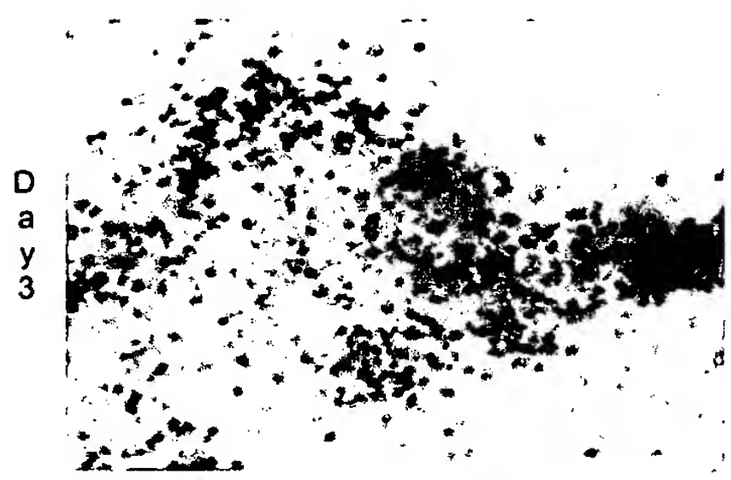
- Petition for Extension (One Month)
- Request for Continued Examination (RCE)
- Appendix
- Declaration by Gila Maor under 1.1.32
- CV of Gila Maor
- Wikipedia for Pyruvate
- Cancedda et al.
- Brown et al.

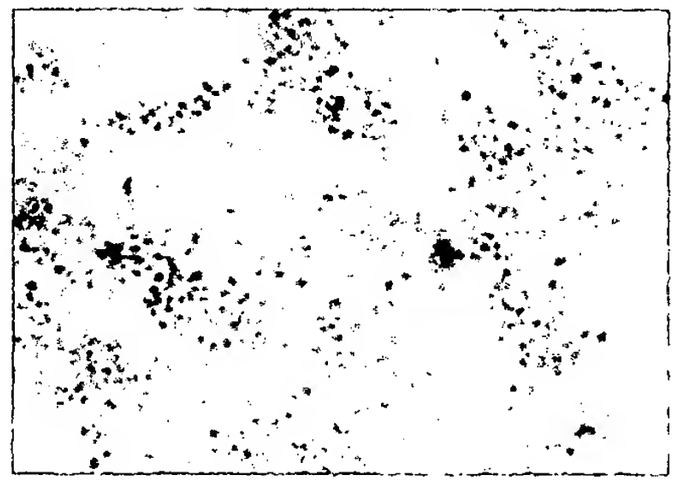
APPENDIX

Chondrocytes isolated from a mandubular condyle as described in pages 43 and 44 of the instant specification were cultured as a monolayer for 3 and 5 days and stained for Type I and Type II collagens, as described in Figure 3 of the instant specification(page 17 lines 6-17).

The following image shows that as soon as 3 days post culturing, mandibular condyle-derived cells cease to produce type I collagen and undergo differentiation into type II collagen expressing cells. Most type II staining is still concentrated intracellularly, while extracellular levels of type II collagen are still low. In the 5 day old culture, however, type II collagen is already present in the intercellular space.

Mandibular Condyle Derived Cells (MCDC); 3 , 5 day old culture





Type II collagen

Type I collagen